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The Correlation of Wear with Histological Features After Failed Hip Resurfacing Arthroplasty

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Investigation performed at the Nuffield Orthopaedic Centre, Oxford, United Kingdom

Background: Tissue necrosis and a macrophage and perivascular lymphocytic infiltrate are commonly seen in periprosthetic tissues around metal-on-metal hip resurfacing implants, including pseudotumors associated with these implants. The purpose of the present study was to correlate pathological changes in periprosthetic tissues with clinical findings and the amount of implant-derived metal wear.

Methods: We analyzed morphological changes in the periprosthetic soft tissues around fifty-six failed metal-on-metal hip resurfacing implants. The most common reason for failure was the presence of a symptomatic pseudotumor (n = 45). The extent of necrosis and the nature of the inflammatory cell infiltrate, including aseptic lymphocyte-dominated vasculitis-associated lesion (ALVAL), was evaluated semiquantitatively. Bearing surface wear was determined for all patients. Prostheses were considered to be highly worn if the total linear wear rate was $\geq 4 \mu\text{m}/\text{yr}$.

Results: Substantial necrosis and a heavy macrophage infiltrate were noted in most periprosthetic tissues, including all pseudotumors, many of which contained a prominent ALVAL infiltrate. Most pseudotumors (80%) were associated with highly worn prostheses. It was noted that the extent of necrosis and macrophage infiltration correlated with the volume of generated metal wear. Although increased wear volume moderately correlated with a high ALVAL response, all pseudotumors associated with low wear had a strong ALVAL response.

Conclusions: The majority of pseudotumors are associated with increased implant wear. This increased wear is associated with soft-tissue necrosis and a heavy nonspecific foreign-body macrophage response coupled with a variable adaptive or specific immune response (ALVAL). A minority of pseudotumors are associated with low wear and a prominent immune response. These findings confirm that minimizing wear from metal-on-metal hip resurfacing arthroplasty prostheses would lead to a reduction in the incidence of pseudotumor. However, a small number of pseudotumors are still likely to occur, which may be due to an exacerbated adaptive immune response.

Level of Evidence: Prognostic Level IV. See Instructions for Authors for a complete description of levels of evidence.

Third-generation metal-on-metal hip resurfacing arthroplasty was introduced in the 1990s, with promising early and intermediate-term reported outcomes¹⁻³. Advances in metal-on-metal manufacturing and tribology have optimized the bearing surfaces, made of high-carbide cobalt (Co), chromium (Cr), and molybdenum (Mo) alloy, to produce minimal wear when functioning optimally⁴. The wear particles that are produced are composed either of chromium

oxide (Cr_2O_3) or CoCrMo; they are of variable nanometer size⁵⁻⁷ and are thought to arise either from the bulk of the material or the tribolayer⁸. Under non-optimum conditions, the amount of wear can dramatically increase, with subsequent implant failure and other complications⁹.

A major complication that occurs following metal-on-metal hip resurfacing arthroplasty is the development of a pseudotumor around the resurfaced hip¹⁰. Concerns about

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higher-than-expected revision rates have led to the recall of the ASR hip prosthesis (DePuy, Warsaw, Indiana) and reports issued by the Medicines and Healthcare products Regulatory Agency (MHRA) in the United Kingdom regarding metal-on-metal hip resurfacing arthroplasty^{11,12}. Although pseudotumors around metal-on-metal hip resurfacing implants occur in association with highly worn prostheses⁹, studies have suggested that pseudotumor formation is not always associated with increased wear¹³⁻¹⁵. This has led to the suggestion that the extensive necrosis and tissue destruction seen in association with pseudotumors around metal-on-metal hip resurfacing implants result not from the cytotoxic effect of the large number of metal particles on macrophages that have phagocytosed these particles¹⁶ but from a hypersensitivity response to one or more metal wear particle components¹⁷. In keeping with this hypothesis, a prominent perivascular lymphoid infiltrate, commonly termed ALVAL (aseptic lymphocyte-dominated vasculitis-associated lesion), is frequently seen in the periprosthetic tissues around metal-on-metal hip implants following both total hip arthroplasty and metal-on-metal hip resurfacing arthroplasty^{10,14,17-20}. This response has led to the hypothesis that delayed hypersensitivity plays an important role in metal-on-metal implant failure^{21,22}. In a previous study, we noted a spectrum of necrotic and inflammatory changes in the periprosthetic tissues around metal-on-metal hip resurfacing implants and concluded that these changes showed features of both a cytotoxic and a hypersensitivity reaction²³. Campbell et al., in a review of the histological findings associated with thirty-two pseudotumors, recently described an ALVAL scoring system based on the morphological features of the synovial lining, tissue organization, and extent of the macrophage, lymphocyte, and other inflammatory cell infiltrate in the periprosthetic tissues around metal-on-metal hip resurfacing implants; when this histological score was correlated with wear, it was found that a higher ALVAL score was associated with low component wear, suggesting that hypersensitivity played the dominant role in pseudotumor formation in these cases¹⁴. The Campbell ALVAL scoring system assesses more than just the extent of the perivascular lymphocyte infiltrate; it includes a number of features that are commonly seen in periprosthetic tissues in response to other implant biomaterials, and its specificity for metal-on-metal hip resurfacing arthroplasty wear has not been validated by other observers.

Whether the inflammatory changes and tissue necrosis seen in periprosthetic tissues around failed metal-on-metal hip resurfacing implants are due to cytotoxicity or hypersensitivity is essential to understanding the pathogenesis of complications related to metal-on-metal hip resurfacing arthroplasty such as pseudotumor. The primary purpose of the present study was to determine whether the amount of prosthesis wear correlated with specific histological features following the failure of metal-on-metal hip resurfacing arthroplasty. Accordingly, we analyzed the extent of necrosis and inflammatory cell infiltration (including ALVAL) in periprosthetic tissues semiquantitatively and correlated these findings with the amount of wear derived from retrieved components.

Materials and Methods

All patients undergoing metal-on-metal hip resurfacing arthroplasty and those requiring revision after the failure of metal-on-metal hip resurfacing arthroplasty at our independent, tertiary referral center (Nuffield Orthopaedic Centre, Oxford, United Kingdom) are prospectively entered into the hospital database. Since 1999, >1550 metal-on-metal hip resurfacing arthroplasties have been performed. Over the same period, 112 revisions of metal-on-metal hip resurfacing arthroplasties have been performed, twenty-two (20%) of which were performed in patients who had had the primary metal-on-metal hip resurfacing arthroplasty elsewhere.

The inclusion criteria for this institutional review board-approved study of revision metal-on-metal hip resurfacing arthroplasty included (1) patient consent for the use of tissue and explants for further study, (2) the availability of explanted prostheses for wear analysis, (3) the availability of tissue for histological examination, and (4) detailed clinical findings for revision mode classification.

Fifty-six hips (fifty-three patients) with metal-on-metal hip resurfacing implants fulfilled the above criteria. Forty-six hips (82%) had had the index metal-on-metal hip resurfacing arthroplasty procedure at our center. Thirty-eight revisions (68%), in thirty-five patients, were in females. All hips had undergone metal-on-metal hip resurfacing arthroplasty for the treatment of osteoarthritis only. The mean duration of implant survival was 4.7 years (range, 0.8 to 9.8 years). Thirty-four failures occurred in patients who had had a unilateral procedure, sixteen failures occurred on one side in patients who had had a bilateral procedure, and six failures occurred on both sides in patients who had had a bilateral procedure. Detailed demographic data are included in the Appendix.

The most common cause of revision was the presence of a symptomatic pseudotumor (n = 45). We define a pseudotumor as a mass that is solid or cystic, or both, that is in communication with the hip joint and is neither neoplastic nor infected^{10,24}. Other modes of failure included periprosthetic femoral neck fracture (n = 5), impingement (n = 2), unexplained pain (n = 2), heterotopic ossification (Brooker type III) (n = 1), and cup loosening (n = 1); the eleven hips with these modes of failure formed the control group. None of the controls had evidence of pseudotumor on preoperative imaging or intraoperatively.

Histological Analysis of Periprosthetic Soft Tissues

The specimens that were submitted for analysis included capsule and synovium, femoral and acetabular pseudomembrane, and, when relevant, pseudotumor. As the size and nature of the lesions varied, the number of specimens submitted could not be standardized and was dependent on gross findings at the time of the operation. The general policy was to sample extensively all involved tissues; the mean number of specimens submitted from each case was six (range, two to thirteen). None of the specimens had histological or microbiological evidence of infection²⁵⁻²⁷.

Hematoxylin and eosin-stained 5- μ m tissue sections were examined and scored by two observers (N.A. and F.M.) who were blinded to the mode of implant failure and the results of wear analysis. All cases were scored with use of the ALVAL scoring system described by Campbell et al. (Campbell-ALVAL)¹⁴. In this system, a score of <4 is defined as low, a score between 5 and 8 is defined as moderate, and a score of 9 or 10 is defined as high. We also assessed tissue necrosis and the extent of the inflammatory cell infiltrate in the periprosthetic tissues around metal-on-metal hip resurfacing implants. The presence of specific inflammatory cells (macrophages, lymphocytes, plasma cells, eosinophil polymorphs) was noted, and the presence or absence of an ALVAL response was also assessed semiquantitatively as previously described^{20,23}; in this scoring system, the number of specific inflammatory cells is scored as 0 (absent), 1+ (few), 2+ (many), or 3+ (abundant). Necrosis was scored as 0 (absent), 1+ (scattered small necrotic areas), 2+ (frequent small or large necrotic areas with up to 25% tissue involvement), or 3+ (extensive necrosis with >25% tissue involvement). The ALVAL response was also graded semiquantitatively as 0 (no evidence of a perivascular lymphocyte infiltrate), 1 (little evidence of a perivascular lymphocytic infiltrate, with lymphocyte cuffing of blood vessels being fewer than five cells in thickness), 2 (several perivascular lymphoid aggregates, with lymphocyte cuffing of vessels being five to ten cells in thickness), or 3 (numerous large perivascular lymphoid aggregates, with lymphocyte

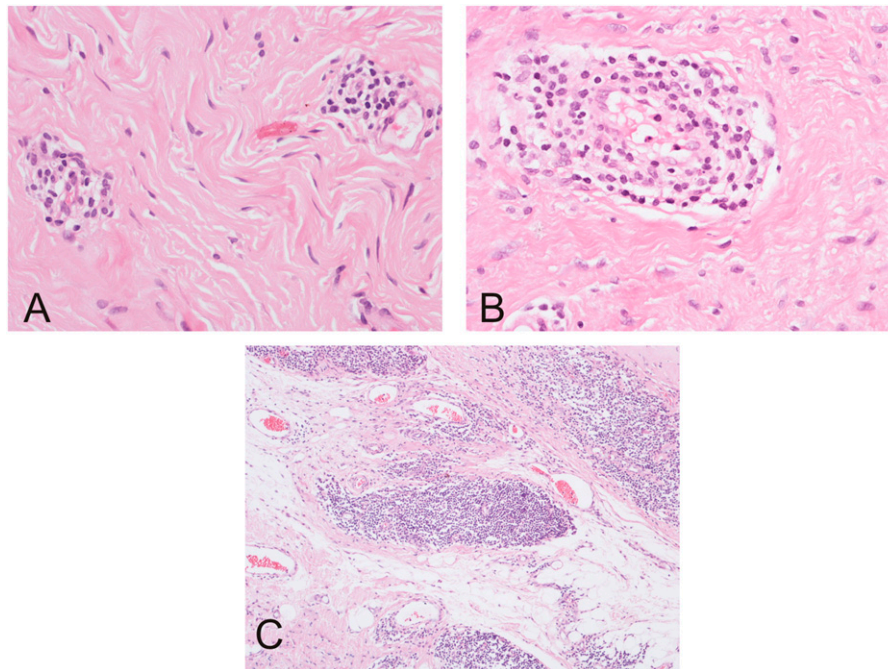


Fig. 1

Figs. 1-A, 1-B, and 1-C Photomicrographs illustrating the Oxford-ALVAL scoring system (hematoxylin and eosin). **Fig. 1-A** Grade 1 (fewer than five lymphocytes around vessels) ($\times 250$). **Fig. 1-B** Grade 2 (five to ten lymphocytes around vessels) ($\times 250$). **Fig. 1-C** Grade 3 (more than ten lymphocytes around vessels) ($\times 40$).

cuffing around vessels being more than ten cells in thickness) (Fig. 1). This scoring system was termed the Oxford-ALVAL score and was assessed in order to provide a single specific quantitative measure of the ALVAL response. As

inflammatory changes are not uniform in periprosthetic tissues, the ALVAL score was based on the maximum perivascular lymphoid infiltrate noted in any one specimen. At least twenty fields per specimen ($100\times$ magnification [$10\times$

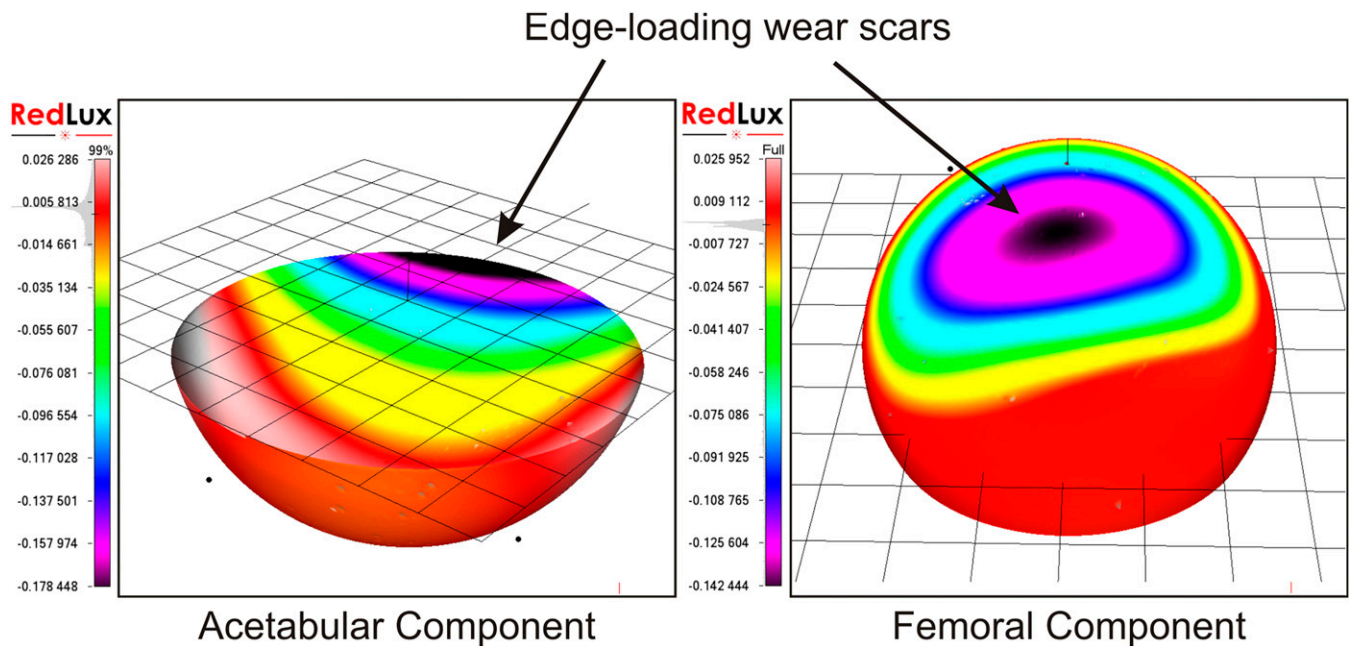


Fig. 2

RedLux images of a metal-on-metal hip resurfacing implant that was revised because of pseudotumor. Of note is the increased wear patch on the edge of the acetabular component, with the associated wear scar on the pole of the femoral head.

objective, 10× eyepiece)) were examined. All cases were scored independently by both reviewers. Repeatability testing demonstrated highly significant intraobserver ($\kappa = 0.86$, $p < 0.001$) and interobserver ($\kappa = 0.74$, $p < 0.001$) (intraclass) correlation coefficients (κ).

Wear Measurement Analysis

All implants were cataloged with an identification number to ensure patient anonymity. Both femoral and acetabular components were available for all patients. Bearing surface wear was assessed with use of a noncontact, optical coordinate measuring system (RedLux, Southampton, United Kingdom) in a blinded fashion at the Smith & Nephew Implant Development Centre (IDC) (Leamington Spa, United Kingdom). The RedLux technique and the measuring system used have previously been validated as a highly accurate method for determining linear and volumetric wear and local radius^{28,29}.

Acetabular component wear measurements were obtained up to the edge of the acetabular component. The presence or absence of edge wear was determined visually after inspection of the wear contours produced. If the wear scar on the acetabular component traversed the edge, edge wear had occurred; in such cases, the wear scar was usually accompanied by a corresponding flattened stripe on the femoral head (Fig. 2). The measurements that were obtained for each femoral and acetabular component included linear wear (μm) and volumetric wear (mm^3). This allowed for the estimation of total (femoral plus acetabular) linear and volumetric wear. Knowing the survival of each metal-on-metal hip resurfacing implant, we were able to calculate the total linear wear rate according to the following formula: total linear wear rate ($\mu\text{m}/\text{yr}$) = total linear wear (μm)/implant survival (yr).

Schmalzried et al. measured the linear wear rate associated with retrieved large head metal-on-metal devices with good outcomes and reported a total linear wear rate of $4 \mu\text{m}/\text{yr}$ ³⁰. Similar observations were reported by

Tuke et al.³¹. Therefore, we defined hips as having high wear rate if the total linear wear rate $\geq 4 \mu\text{m}/\text{yr}$. On the contrary, hips with total linear wear rate $< 4 \mu\text{m}/\text{yr}$ were considered to be associated with low/expected prosthesis wear.

Reliability of Wear Measurements

The reliability of the particular optical profilometry method to estimate linear wear was tested against a roundness machine (Talyrond 290; Taylor Hobson, Leicester, United Kingdom). The average difference (and standard deviation) between the two methods was $0.08 \pm 0.43 \mu\text{m}$. Similarly, the reliability of the RedLux system to estimate volumetric wear was compared with a gravimetric method with use of a precision balance (Mettler Toledo 500; Mettler Toledo, Leicester, United Kingdom). The RedLux-estimated wear volume was compared with the measured wear volume; the average difference was $0.01 \pm 0.01 \text{ mm}^3$.

Analysis

The revisions were grouped, according to indication, into those that were due to pseudotumor (pseudotumor group) and those that were due to other indications (control group). The amount of wear, the total linear wear rate, and the prevalence of histological findings for different revision groups were assessed. In addition, the associations between histological findings and the amount of wear as well as the total linear wear rate were tested. The determined ALVAL scores (Campbell-ALVAL and Oxford-ALVAL scores) were tested for correlation with the total linear wear rate.

The nonparametric Mann-Whitney U and Kruskal-Wallis tests were used to calculate the level of significance of the differences between the non-normally distributed linear and volumetric wear amounts associated with different histological findings. Cross-tabulated data were compared with use of

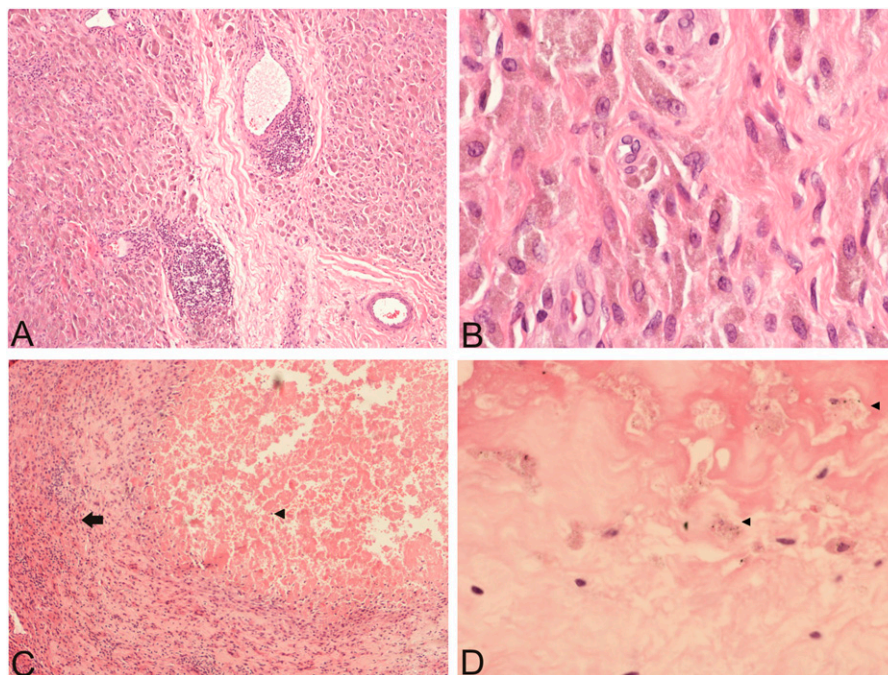


Fig. 3

Figs. 3-A through 3-D Photomicrographs showing the variable cell and tissue response to Co-Cr particles (hematoxylin and eosin). **Fig. 3-A** A heavy (3+) infiltrate of wear particle-containing macrophages and perivascular lymphocytes in periprosthetic tissues ($\times 40$). **Fig. 3-B** High-power view of viable macrophages containing Co-Cr particles ($\times 400$). **Fig. 3-C** A cystic pseudotumor containing viable wear particle-containing macrophages (arrow) in the wall with necrotic macrophages (arrowhead) on the surface ($\times 40$). **Fig. 3-D** High-power view of the surface of a pseudotumor showing macrophages, some of which are necrotic but still contain Co-Cr particles (arrowheads) ($\times 400$).

TABLE I Histological Findings and Total Linear Wear Rate

Histological Findings (no. of hips)				Total Linear Wear Rate (no. of hips)		
Score	Pseudotumor Group (N = 45)	Control Group (N = 11)	P Value	>4 $\mu\text{m}/\text{yr}$ (N = 39)	$\leq 4 \mu\text{m}/\text{yr}$ (N = 17)	P Value
Campbell-ALVAL						
Necrosis			<0.001			0.001
0 to 1	3	5		1	7	
2 to 3	42	6		38	10	
Macrophages			<0.001			0.006
0 to 1	1	8		2	7	
2 to 3	44	3		37	10	
Lymphocytes			0.001			0.04
0 to 1	13	9		14	8	
2 to 3	32	2		25	9	
Total			<0.001			0.003
0 to 4	1	6		1	6	
5 to 8	29	4		26	7	
9 to 10	15	1		12	4	
Oxford-ALVAL						
0	2	8	<0.001	2	8	0.002
1	6	2		7	1	
2	12	1		10	3	
3	25	0		20	5	

the chi-square (χ^2) test. The Spearman correlation coefficient (ρ) was used to assess correlation between histological features, ALVAL scores (Campbell and Oxford), and the amount of wear detected and the total linear wear rate calculated. Correlation was characterized as poor (0.00 to 0.20), fair (0.21 to 0.40), moderate (0.41 to 0.60), good (0.61 to 0.80), or excellent (0.81 to 1.00). The level of significance was set at $p < 0.05$. Statistical analysis was performed with the SPSS statistical program (version 18.0; SPSS, Chicago, Illinois).

Source of Funding

Financial support has been received from the NIHR Biomedical Research Unit. Funds were only used for supplies. No other funds have been received relevant to this project by any member of this team.

Results

Histological Findings in Periprosthetic Tissues Around Metal-on-Metal Hip Resurfacing Implants

All but two of the fifty-six hips had positive histological findings on review. As noted in previous studies^{14,20,23}, there was a wide spectrum of histological findings, including a variable, often prominent, perivascular lymphoid infiltrate, tissue necrosis, and macrophage response (Fig. 3). Necrosis was seen in all cases, with the majority of patients showing 2+ ($n = 13$) or 3+ ($n = 35$) necrosis. Necrotic areas were composed of necrotic connective tissue and often contained numerous macrophages that had undergone necrosis. Necrosis was most prominent on the surface of the sampled periprosthetic tissues. A heavy (2+ [$n = 9$] or 3+ [$n = 38$]) macrophage infiltrate was noted in most cases. The lymphocyte response was more variable, with 1+ ($n = 17$), 2+ ($n = 9$), or 3+ ($n = 25$) infiltration

being noted in most cases; a few cases ($n = 5$) contained no obvious lymphocyte infiltrate. The amount of necrosis had good correlation with the extent of macrophage infiltration ($\rho = 0.62$, $p < 0.001$) and moderate correlation with the amount of lymphocyte infiltration ($\rho = 0.5$, $p < 0.001$). The lymphocyte infiltrate was mainly perivascular in distribution, and its extent closely mirrored the Oxford-ALVAL score ($\rho = 0.73$, $p < 0.001$). A prominent plasma cell infiltrate was seen in eight cases. Eosinophil polymorphs were only seen in four cases. Analysis of the ALVAL response with use of the previously described Campbell-ALVAL scoring system resulted in a mean score of 7.5 (range, 3 to 9); the majority of hips ($n = 51$; 91%) had a Campbell-ALVAL score of ≥ 6 . The Oxford-ALVAL score was also high (≥ 2) in most cases ($n = 38$; 68%).

The extent of necrosis, macrophage infiltration, and lymphocyte infiltration, as assessed with the Campbell-ALVAL and Oxford-ALVAL scores, was significantly higher in the pseudotumor group than in the control group ($p < 0.002$) (Table I). In the majority of hips in the pseudotumor group, there was substantial (2+/3+) necrosis ($n = 42$) and macrophage infiltration ($n = 44$). The extent of the lymphocyte response, however, was more variable, although the majority of cases had moderate or strong lymphocyte infiltration ($n = 32$; 71%); a low or unsubstantial lymphocyte infiltrate was detected in thirteen cases (29%). No difference in histological features was seen between unilateral and bilateral metal-on-metal hip resurfacing implants that were revised because of pseudotumor ($p = 0.2$ to 0.8).

TABLE II Wear Analysis

	Pseudotumor Group (N = 45)	Control Group (N = 11)	P Value
Linear wear (μm)			
Femur			<0.001
Mean and standard deviation	43.3 \pm 58.5	6.4 \pm 8.6	
Range	0.0 to 283.1	0.0 to 23.5	
Cup			0.02
Mean and standard deviation	97.7 \pm 207.8	9.2 \pm 14.1	
Range	0.0 to 948.9	0.0 to 60.7	
Total			0.004
Mean and standard deviation	140.9 \pm 243.5	14.8 \pm 23.4	
Range	0.0 to 987.4	0.0 to 60.7	
Volumetric wear (mm^3)			
Femur			<0.001
Mean and standard deviation	19.1 \pm 39.4	1.7 \pm 2.3	
Range	0.0 to 197.8	0.0 to 5.9	
Cup			0.03
Mean and standard deviation	12.8 \pm 29.1	1.0 \pm 1.3	
Range	0.0 to 149.9	0.0 to 2.7	
Total			0.007
Mean and standard deviation	32.4 \pm 69.9	2.3 \pm 3.5	
Range	0.0 to 347.7	0.0 to 8.6	
Total linear wear rate ($\mu\text{m}/\text{yr}$)			<0.001
Mean and standard deviation	26.4 \pm 40.3	2.9 \pm 4.3	
Range	0.0 to 201.5	0.0 to 12.8	
No. of hips with total linear wear rate $>4 \mu\text{m}/\text{yr}$	37 (82%)	2 (18%)	<0.001
Total volumetric wear rate (mm^3/yr)			0.002
Mean and standard deviation	5.5 \pm 10.4	0.4 \pm 0.5	
Range	0.0 to 48.3	0.0 to 1.4	
No. of hips with edge-loaded scars	37 (82%)	4 (36%)	0.002

TABLE III Correlation of Total Linear Wear Rate with Histological Features

	Correlation*				
	Necrosis	Macrophages	Lymphocytes	Campbell-ALVAL	Oxford-ALVAL
Total linear wear rate	0.45 (p < 0.001)	0.43 (p < 0.001)	0.33 (p < 0.13)	0.16 (p < 0.26)	0.41 (p < 0.002)

*The values are given as the Spearman rho coefficient, with the p value in parentheses.

Wear Analysis

The mean femoral component linear wear was 36 μm (range, 0 to 283 μm), and the mean acetabular component linear wear was 87 μm (range, 0 to 949 μm). The mean femoral component volumetric wear was 15.6 (range, 0 to 198 mm^3), and the mean acetabular component volumetric wear was 11.3 mm^3 (range, 0 to 150 mm^3). The linear and volumetric wear parameters of both components showed moderate/good correlation with implant survival time ($\rho = 0.44$ to 0.66 ; $p < 0.001$). The total

linear wear rate was 21.8 $\mu\text{m}/\text{yr}$ (range, 0 to 202 $\mu\text{m}/\text{yr}$). The majority of prostheses ($n = 39$; 70%) had total linear wear rate of $>4 \mu\text{m}/\text{yr}$. Edge loading was detected in the majority of components ($n = 41$; 73%). Components that were revised because of pseudotumor had significantly higher wear compared with components that revised because of other modes of failure ($p < 0.001$). The majority of hips in the pseudotumor group ($n = 37$; 82%) had high total linear wear rate, whereas only two of the hips in the control group had high total linear wear rate

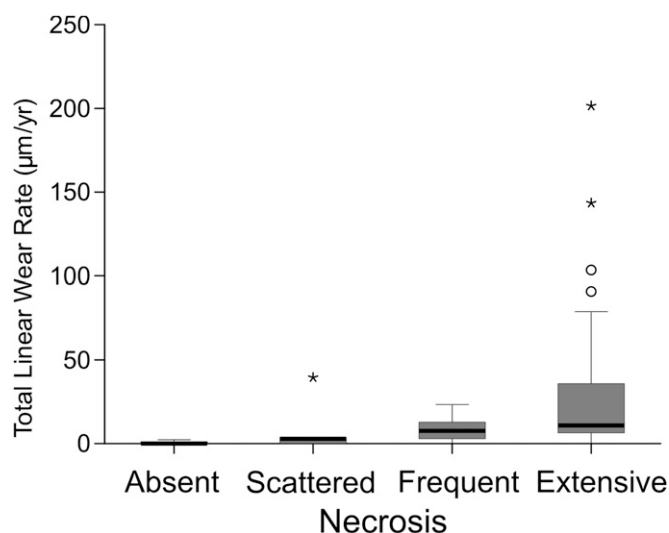


Fig. 4
Box-plot diagram of the total linear wear rate plotted against the histological evaluations of necrosis for the entire cohort.

(Table II). There was no difference in wear measurements between pseudotumors identified around unilateral metal-on-metal hip resurfacing implants and those identified around bilateral ones ($p = 0.7$).

Correlation of Histological Features with Wear Measurements

Histological findings did not strongly correlate with wear measurements (Tables I and III). The extent of necrosis and macrophage infiltration moderately correlated with the total linear wear rate. Hips that exhibited extensive necrosis and a heavy macrophage infiltrate were associated with the greatest total linear wear rate (Fig. 4) (see Appendix). However, some hips ($n = 10$) had a low total linear wear rate and moderate or strong necrosis and macrophage infiltration (score, 2 or 3). The majority of these hips ($n = 8$) were in the pseudotumor group. The presence of lymphocytes was associated with a significantly greater total linear wear rate (see Appendix). However, some hips ($n = 9$) had a low total linear wear rate and a prominent lymphocyte presence. Eight of these hips were in the pseudotumor group (see Appendix). The Campbell-ALVAL score did not correlate with the total linear wear rate ($p = 0.3$) (see Appendix). However, hips with low Campbell-ALVAL scores had significantly less wear in comparison with those with both moderate ($p = 0.002$) and high scores ($p = 0.008$). The Oxford-ALVAL score correlated weakly with the total linear wear rate ($\rho = 0.4$; $p = 0.002$) (Table III).

Discussion

In the present study, we found that necrotic and inflammatory changes are commonly found in the periprosthetic tissues around metal-on-metal hip resurfacing implants, especially in patients with pseudotumors, and that both necrosis and the extent of the macrophage infiltrate correlate moderately

with the extent of prosthesis wear. The extent of the perivascular lymphocyte reaction (ALVAL), which presumably reflects the specific or adaptive immune response, also correlated moderately with the amount of wear in metal-on-metal hip resurfacing arthroplasty cases. A small number of hips in the pseudotumor group that had relatively low wear had a heavy ALVAL response. However, a small number of hips in the pseudotumor group with high wear had minimal ALVAL response. These findings indicate that most pseudotumors are associated with increased wear, necrosis, and a pronounced ALVAL response. A few hips exhibited a histological reaction that did not follow this paradigm; this finding may reflect variability in the individual response to the amount and, possibly, type of metal debris.

The pathological changes in the periprosthetic tissues around metal-on-metal hip resurfacing implants are well characterized^{14,23}. These changes include extensive necrosis, loss of the synovial lining, a heavy macrophage response to metal wear particles, and a pronounced perivascular lymphoid infiltrate composed mainly of lymphocytes. We noted considerable necrosis in revised metal-on-metal periprosthetic tissues and found that this was invariably associated with a heavy macrophage infiltrate. Our analysis demonstrated that both necrosis and the macrophage infiltrate showed moderate correlation with the amount of prosthesis-derived wear. These findings suggest that the extent of this innate, nonspecific (foreign body macrophage-associated) response is related to the amount of prosthesis wear. Metal-on-metal hip resurfacing arthroplasty-derived metal wear particles, particularly cobalt, are likely to have a cytotoxic effect on phagocytic macrophages^{16,32-34}. This could lead to a vicious cycle in which metal wear particle generation leads to a foreign body macrophage response; the inability of macrophages to process the phagocytosed particles would result in cell death with re-release of the metal wear particles, leading to further macrophage recruitment and continuation of the cycle. Release of lysosomal enzymes from the necrotic macrophage component may contribute to the extensive connective tissue destruction seen in association with pseudotumors³³. Surface ulceration of the pseudocapsule and pseudomembrane around metal-on-metal hip resurfacing implants is commonly seen and may reflect this process; the cells that line the surface of periprosthetic tissues are mainly macrophages and these phagocytes would be expected to encounter the highest concentration of prosthesis-derived metal particles. It has been shown that exposure of articular synovial tissues to Co-Cr debris can lead to surface ulceration in the absence of a loose prosthesis³⁵. Macrophages have also been shown to detoxify Co-Cr particles, resulting in less cytotoxicity and genotoxicity compared with fibroblasts that internalize these particles³⁶.

A perivascular lymphocyte reaction has been noted in the periprosthetic tissues around metal-on-metal hip resurfacing implants that have failed; this reaction is considered to develop as a result of a hypersensitivity response to Co-Cr metal wear debris. The Oxford-ALVAL score was moderately correlated with the total linear wear rate. Although an ALVAL response

was seen in the periprosthetic tissues around metal-on-metal hip resurfacing implants demonstrating both low wear and high wear, most (twenty) of the twenty-five hips with an Oxford-ALVAL score of 3 had highly worn metal-on-metal hip resurfacing implants. The perivascular lymphocyte reaction that characterizes ALVAL is thought to represent part of an adaptive immune response^{14,18,20}. It has been suggested that this response could represent a form of lymphoid neogenesis associated with vascular changes that would produce variable tissue necrosis³⁷. The pathological features seen in association with the failure of metal-on-metal hip resurfacing arthroplasty include a heavy macrophage infiltrate with the formation of granulomas, tissue necrosis, and a prominent lymphoid infiltrate. These changes are suggestive of a delayed hypersensitivity (Type-IV) reaction. The lymphocyte population associated with the failure of

failed surface implants comprises mainly CD3+ T lymphocytes along with a mixture of CD4+ and CD8+ cells^{20,23}. These cells play a role in the recruitment of macrophages and, as in other delayed hypersensitivity reactions, the extent of the lymphocyte response (and consequent macrophage infiltration and tissue necrosis) is antigen-dependent. Our findings also suggest that the adaptive immune response to metal wear particles plays an important role in the failure of metal-on-metal hip resurfacing implants as not all pseudotumors were associated with high wear ($n = 8$). As the ability of an individual to respond to immunogens varies³⁸, some patients may develop an immune response at low/expected wear levels. However, when the amount of wear increases, the risk of exceeding the immune threshold and hence evoking an ALVAL response is correspondingly increased. Further research is needed to

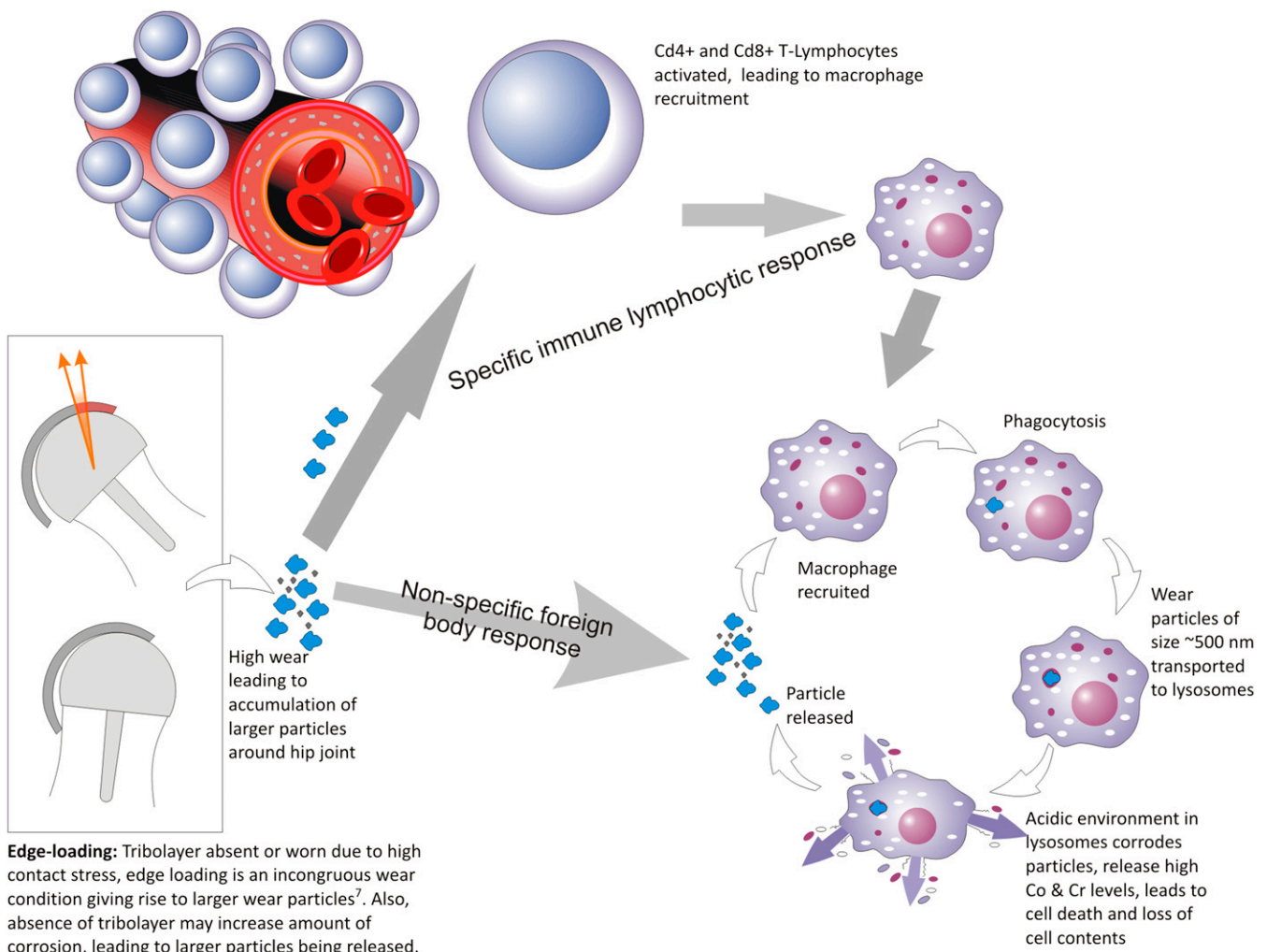


Fig. 5

Schematic of the pathogenetic mechanisms proposed to be involved in pseudotumor development. Metal wear particles in periprosthetic tissues stimulate a nonspecific innate foreign-body response and a specific or adaptive immune response. The innate response involves the recruitment of phagocytic macrophages to the area of wear-particle deposition; inability to process the particles (especially cobalt) results in cell death and the release of lysosomal enzymes (causing tissue damage) and metal particles, leading to further macrophage recruitment and repetition of this cycle. The adaptive immune response to metal particles involves the activation of T lymphocytes, which promote macrophage recruitment.

preoperatively identify patients who may have a low immunogenicity threshold and are likely to develop a pronounced reaction to a metal-on-metal hip resurfacing implant. The macrophage response to Co-Cr and other metallic or polymeric wear particles is largely dependent on the size of the particles³⁹. Where the particles are large, they produce a typical foreign-body reaction with accumulation of macrophages and giant cells around a large wear particle; this may occur when the tribolayer has been disturbed under edge-loading conditions. Where the particles are small, during optimal metal-on-metal tribological conditions, they can be phagocytosed and processed by macrophages. As shown in Figure 5, the effect of the nonspecific foreign-body response and the adaptive immune response to Co-Cr wear particles are unlikely to be mutually exclusive; both mechanisms are likely to play a role in pseudotumor formation. As particles alone cannot directly interact with immune cells, the precise mechanism whereby T cells are activated by Co-Cr particles is not certain; it would appear that this particle reaction, however, is not unique to Co-Cr as perivascular and diffuse lymphocytic inflammation and necrosis have been noted in association with other types of wear particles, both metallic and polymeric⁴⁰.

Among the forty-five hips in the pseudotumor group, eight (18%), had a low Oxford-ALVAL score (0 to 1), a high total linear wear rate, necrosis, and macrophage response, indicating a predominantly innate, nonspecific foreign-body response; eight (18%) had a high Oxford-ALVAL score (2 to 3) and a low total linear wear rate, indicating a predominantly adaptive immune response; and the remaining twenty-nine (64%) had a high total linear wear rate, necrosis, and a 2+ or 3+ macrophage and perivascular lymphocytic response, indicating the presence of both an innate foreign body response and an adaptive immune response. These findings suggest that decreasing the amount of wear from metal-on-metal components could reduce the frequency of pathological changes associated with pseudotumor formation. Thus, surgeons should aim to minimize wear from metal-on-metal prostheses with appropriate patient/implant selection and surgical technique.

This retrospective study had a number of limitations. The number of hips in the pseudotumor group was greater than that in the control group. This disparity in numbers was due to limitations in resources, and it was decided that greater insight would be provided by studying a larger number of hips with pseudotumors. Second, tissue for histological assessment was obtained according to the discretion of the surgeon, and hence sampling errors could have been made. However, all procedures were performed by hip surgeons with considerable experience in revision surgery. Last, wear analysis based on the total linear wear rate has certain inherent limitations. Analysis is limited to estimating the local deepest scar and not the mean amount of wear. Furthermore, although metal-on-metal wear has a biphasic rate⁴¹, the calculation of the total linear wear rate determines a mean value without accounting for the difference between the two phases.

However, correlations between histological features and wear were similar, regardless of the wear-measurement method tested.

Our findings contrast with those of Langton et al.⁴², who did not establish an association between lymphocyte infiltration and wear volume. The number of cases in their study, however, was relatively small, and this may have been a limiting factor. Our morphological findings are similar to those of Campbell et al.¹⁴, but we found that the ALVAL scoring system that they proposed did not provide sufficiently well-defined or discriminatory criteria to permit distinction between high-wear and low-wear metal-on-metal hip resurfacing implants. That scoring system assesses several cell and tissue components to provide a total score that characterizes the response to metal-on-metal wear. Two of the main criteria of that scoring system are the status of the synovial lining and tissue organization. In the present study, loss of the synovial lining was commonly found in the periprosthetic tissues around both low and high-wear metal-on-metal hip resurfacing implants, and we also noted a marked loss of normal arrangement (Campbell-ALVAL score 2) and perivascular lymphocyte aggregates (Campbell-ALVAL score 3) in most specimens. The latter finding overlaps with another major criterion of that scoring system, i.e., the extent of the macrophage and lymphocyte infiltrate; the evaluation of the extent of infiltration by these inflammatory cells is used effectively to reflect the nonspecific and specific or adaptive response to wear particles, respectively. However, the findings of our own and previous studies^{14,18,20,22,23} indicate that these two inflammatory cell components are commonly found in the periprosthetic tissues around metal-on-metal hip resurfacing implants. The Oxford-ALVAL score, which measures the single histological feature that corresponds to the original description of ALVAL (i.e., the extent of lymphocyte cuffing around vessels), provides a semi-quantitative measure of the adaptive immune response²⁰; it is much easier to evaluate and in effect combines the second and third criteria of the Campbell-ALVAL system.

Appendix

eA A table showing demographic data on the pseudotumor and control groups and diagrams plotting the total linear wear rate against the presence of macrophages, lymphocytes (entire cohort), lymphocytes (pseudotumor group), the Campbell-ALVAL score, and the Oxford-ALVAL score are available with the online version of this article as a data supplement at jbjs.org. ■

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